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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/00</b>		<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 99/45905</b> <b>(43) International Publication Date:</b> 16 September 1999 (16.09.99)
<b>(21) International Application Number:</b> PCT/US99/04650 <b>(22) International Filing Date:</b> 11 March 1999 (11.03.99) <b>(30) Priority Data:</b> 60/078,001 13 March 1998 (13.03.98) US <b>(71) Applicant (for all designated States except US):</b> POZEN INC. [US/US]; Suite 240, 6330 Quadrangle Drive, Chapel Hill, NC 27514 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> PLACHETKA, John, R. [US/US]; 321 Silver Creek Trail, Chapel Hill, NC 27514 (US). <b>(74) Agent:</b> SANZO, Michael, A.; Vinson & Elkins L.L.P., 2300 First City Tower, 1001 Fannin, Houston, TX 77002-6760 (US).			<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> PROPHYLAXIS AND TREATMENT OF MIGRAINE HEADACHES WITH THROMBOXANE SYNTHETASE INHIBITORS AND/OR RECEPTOR ANTAGONISTS			
<b>(57) Abstract</b> <p>The use of thromboxane receptor antagonists and/or thromboxane synthetase inhibitors in the prophylaxis and treatment of migraine is described. Further described are the use of thromboxane receptor antagonists and/or thromboxane synthetase inhibitors together with known migraine palliatives such as 5-HT<sub>1</sub> agonists, non-steroidal anti-inflammatory agents, and the like. Pharmaceutical compositions are described containing both known migraine palliatives and thromboxane receptor antagonists and/or thromboxane synthetase inhibitors.</p>			

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## Prophylaxis and Treatment of Migraine Headaches with Thromboxane Synthetase Inhibitors and/or Receptor Antagonists

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### Background of the Invention

Migraine headaches represent a well-known and well-characterized affliction. Many patients have a readily diagnosed susceptibility to the development of migraine headaches for which known drug therapies attempt either to prevent or reduce the number of migraine headaches or mitigate their debilitating effects on the patient. Examples of agents that are known to be useful in either the prophylaxis or palliation of migraine headaches include beta-adrenergic receptor blocking agents like propranolol (Diamond, S. et al., Long-term study of propranolol in the treatment of migraine. *Headache*, 22:268-271, 1982), tricyclic antidepressants like amitriptyline (Ziegler, D.K. et al., Migraine prophylaxis. A comparison of propranolol and amitriptyline. *Arch. Neurol.*, 44:486-489, 1987), calcium antagonists such as flunarizine (Diamond, S. and Freitag, F.G. A double blind trial of flunarizine in migraine prophylaxis. In: *New Advances in Headache Research*: 2: 349-254, 1991, Clifford Rose, F. (Ed.), Smith-Gordon: London), divalproex sodium (Hering, R. and Kuritzky, A. Sodium valproate in the prophylactic treatment of migraine: A double-blind study versus placebo. *Cephalalgia*, 12:81-84, 1992), non-steroidal anti-inflammatory agents like naproxen sodium (Bellavance, A.J. and Meloche, J.P. A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. *Headache*, 30:710-715, 1990), ergotamine and dihydroergotamine (Young, W.B. Appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine: current perspectives. *Headache*, 37(suppl. 1):S42-S45, 1997), and serotonin-1d receptor agonists like sumatriptan (Cady, R.K. et al., Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*, 265:2831-2835, 1991).

Arachadonic acid is known to produce a number of metabolites, including prostacyclin, prostaglandins, lipoxins, and thromboxanes. Thromboxane A<sub>2</sub> is synthesized by the thromboxane synthetase enzyme, located in part in the blood platelets. Thromboxane A<sub>2</sub> is a powerful vasoconstrictor, bronchoconstrictor, pro-inflammatory, and pro-aggregatory substance; as such, its actions are in direct opposition to those of the vasodilatory and anti-thrombotic eicosanoid prostacyclin.

Pharmacological agents capable of preventing the formation of some or all of these metabolites are known, *e.g.*, cyclooxygenase inhibitors and prostaglandin synthetase inhibitors.

Similarly known are thromboxane synthetase inhibitors. Known thromboxane synthetase inhibitors include camonagrel, CGS-12970, E-6700, FCE-27262, imitrodest (CS-518), isbogrel (CV-4151), KK-505, KY-063, nafagrel (DP-1904), ozagrel (OKY-046), pirmagrel (CGS-13080), rolafagrel (FCE-22178) and satigrel (E-5510).

5 Also known are thromboxane receptor antagonists. Thromboxane receptors themselves are known and have been characterized. "Thromboxane receptor antagonists" are pharmacological agents capable of acting as antagonists to thromboxane receptors (DeMais, R. et al., Thromboxane A<sub>2</sub> receptor antagonists, synthesis and activities of phenylsulfonamido derivatives. Eur. J. Med. Chem., 26:821-827, 1991; Maconochie, J. et al.,  
10 Evaluation of the vascular thromboxane A<sub>2</sub> receptor blocking activity of GR32191 in man. Proc. Brit. Pharmacol. Soc., 662P, Jul. 6-8, 1988; Lumley, P. et al., The effects of GR32191, a new thromboxane receptor blocking drug, on platelets and vascular smooth muscle *in vitro*. Thromb. Haemo-stas., 58:261, 1987). Examples of these receptor antagonists include daltroban (BM-13505), domitroban, F-10171, FR-106881, ICI-192605, ifetroban (BMS-180291), KT-  
15 2962, linotroban (HN-11500), mipitroban (UP-11677), ON-579, ramatroban (BAY-u-3405), S-17732, seratrodest (AA-2414), SKF-88046, SQ-30741, sulotroban (BM-13177), and vapirost (GR32191).

Also known are compounds which combine the activities of thromboxane synthetase inhibition and thromboxane receptor blockade in a single molecule. These compounds  
20 potentially provide the advantage of increasing the tissue levels of prostacyclin while inhibiting the formation and activity of thromboxane A<sub>2</sub>. Examples of these receptor antagonists include BIBU-308, ICI-D1542, CGS-22652, GR85305, ridogrel (R-68070), TER-930180, and ZD-9583.

A number of pharmacological effects or actions have been reported for both  
25 thromboxane receptor antagonists and thromboxane synthetase inhibitors. These include: (a) inhibition of the *in vitro* and *in vivo* vasoconstrictor and platelet aggregating effects of endogenous thromboxane A<sub>2</sub>, and exogenously administered arachadonic acid and the prostaglandin analog U46619 (Templeton, A.G.B. et al., The role of endogenous thromboxane in contractions to U46619, oxygen, 5-HT and 5-ct in the human isolated umbilical artery. Br.  
30 J. Pharmacol., 103:1079-1084, 1991; Hirata, Y. et al., Roles of platelet-activating factor, thromboxane A<sub>2</sub>, ADP and thrombin in thrombogenesis in the guinea pig. Eur. J. Pharmacol.,

231:421-425, 1991); (b) inhibition of allergen- and mediator-induced bronchoconstriction (Beasley, R.C.W. et al., Effect of a thromboxane receptor antagonist on PGD<sub>2</sub>- and allergen-induced bronchoconstriction. *J. Appl. Physiol.*, 66:1685-1693, 1989; Myou, S. et al., Inhibitory effect of a selective thromboxane synthetase inhibitor, OKY-046, on acetaldehyde-induced bronchoconstriction in asthmatic patients. *Chest*, 106:1414-1418, 1994), and; (c) prevention of coronary artery reocclusion after thrombolytic therapy (Fitzgerald, D.J. and FitzGerald, G.A. Role of thrombin and thromboxane A<sub>2</sub> in reocclusion following coronary thrombolysis with tissue-type plasminogen activator. *Proc. Natl. Acad. Sci.*, 86:7585-7589, 1989).

## 10 Summary of the Invention

The present invention provides novel pharmaceutical compositions and method for the treatment and/or prophylaxis of migraine headaches. The present invention particularly relates to:

(a) a method for preventing or treating a migraine headache in a patient susceptible to the development of migraine headaches or experiencing a migraine headache, which comprises:

administering to said patient an amount of one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors effective to reduce the severity or duration of or prevent the occurrence of or mitigate the effects of a migraine headache;

(b) a method for treating a migraine headache as described in (a) above, which further comprises:

concomitantly administering to said patient an amount of one or more pharmacological agents selected from the group consisting of beta-adrenergic receptor blocking agents, tricyclic antidepressants, calcium antagonists, divalproex sodium, ergots and dihydroergotamine, serotonin receptor agonists, methylxanthines, non-steroidal anti-inflammatory agents, and dopamine agonists such as metoclopramide and domperidone, effective in combination with said one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors to reduce the severity or duration of a migraine headache;

(c) a pharmaceutical composition comprising:

(1) an amount of one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors; and

(2) an amount of one or more pharmacological agents selected from the group consisting of beta-adrenergic receptor blocking agents, tricyclic antidepressants, calcium antagonists, divalproex sodium, ergots and dihydroergotamine, serotonin receptor agonists, methylxanthines, non-steroidal anti-inflammatory agents, and dopamine agonists such as metoclopramide and domperidone, effective in combination with said one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors to reduce the severity or duration of a migraine headache;

(d) in a method of treating a migraine headache, which consists essentially of administering to a patient suffering from a migraine headache a known migraine palliative selected from the group consisting of beta-adrenergic receptor blocking agents, tricyclic antidepressants, calcium antagonists, divalproex sodium, ergots and dihydroergotamine, serotonin receptor agonists, methylxanthines, and dopamine agonists such as metoclopramide and domperidone, the improvement which comprises:

concomitantly administering to said patient an amount of one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors effective in combination with said known migraine palliative to reduce the severity or duration of said migraine headache.

In accordance with the present invention, there is administered to a human suffering from a migraine headache an amount of one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors, either alone or in combination with one or more known migraine palliatives, to reduce the severity or duration of said migraine headache. Further, the present invention provides additionally for the prophylaxis of migraine headaches in patients susceptible to the development of migraines whereby the severity or duration of migraine headaches is reduced in such susceptible patients.

The present invention therefore contemplates that the administration of the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors will be accomplished by any systemic route which is convenient and readily accessible to the attending physician. While all of the various conventional routes of administration are contemplated (e.g., intramuscular, subcutaneous, intravenous, intranasal, transdermal, vaginal, rectal, buccal and oral), the preferred route of administration (to the extent feasible) is orally by means of a convenient oral dosage form. By this preferred embodiment, an oral dosage form, either solid (e.g., compressed tablets or gelatin capsules) or liquid (syrups or elixirs), is prepared by conventional methods.

Most preferably, simple compressed tablets containing the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors, alone or together with known migraine palliatives, is prepared.

The present invention further contemplates the use of thromboxane receptor antagonists and/or thromboxane synthetase inhibitors as an adjunct to conventional migraine therapy with  
5 known migraine palliatives, specifically providing for the administration of thromboxane receptor antagonists and/or thromboxane synthetase inhibitors concomitantly with such known palliatives.

In accomplishing the purposes of the present invention "concomitant" administration  
10 refers to the administration of the two agents (i.e., the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors and known palliatives) in any manner in which the pharmacological effects of both are manifest in the migraine patient at the same time. Thus, concomitant administration does not require that a single pharmaceutical composition, the same dosage form, or even the same route of administration be used for administration of both the  
15 thromboxane receptor antagonists and/or thromboxane synthetase inhibitors and the known palliative or that the two categories of agents be administered at precisely the same time. However, the concomitant administration will be accomplished most conveniently by the same dosage form and the same route of administration, at substantially the same time. Obviously, the concomitant administration most advantageously proceeds by the administration of the  
20 thromboxane receptor antagonists and/or thromboxane synthetase inhibitors and the known palliative simultaneously in a novel pharmaceutical composition in accordance with the present invention.

The present invention further provides that the amount of the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors to be administered to a migraine patient  
25 be effective to inhibit *in vivo* the formation of or the pharmacological action of thromboxanes in the central nervous system. Just as doses of the known migraine palliatives must be carefully titrated in a migraine patient, the amount of the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors effective to inhibit thromboxane effects must likewise be carefully titrated on a patient-by-patient basis, taking into account the age, weight, condition  
30 and sex of the patient, and the severity of the migraine attack (or need for prophylaxis). Equally importantly, the migraine patient's prior therapy must be evaluated (e.g., reaction to

conventional anti-migraine therapies), in order to establish the extent by which the dose of such conventional migraine palliatives may be diminished as therapy with thromboxane receptor antagonists and/or thromboxane synthetase inhibitors is initiated.

For a typical migraine patient the ultimate dosage of the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors which will effectively inhibit the *in vivo* action of thromboxanes is on the order of 0.1 to about 2500 mg, preferably 2 to 2000 mg, per day, administered orally in single or divided doses. When patient response in this dosage range is insufficient, somewhat higher doses of the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors are employed, ordinarily not in excess of 3200 mg per patient per day administered orally. When other routes of administration are employed, the equivalent dosages to the aforementioned dosages are employed. Equivalent dosages refer to those dosages by such other routes whereby comparable systemic levels (e.g., blood levels) of the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors are obtained.

By the preferred route of administration, which is oral administration, the desired dosage is ordinarily provided in a unit dosage form periodically throughout the day. For the prophylactic treatment of migraine headaches, the desired unit dosage is administered one to six times daily, preferably one to three times daily, on a continuous basis. For the therapeutic treatment of a migraine headache attack, the desired unit dosage is administered at the first signs or symptoms of the migraine attack, and repeated every two to twelve hours, preferably every four to six hours, for a duration of up to seventy two hours or until the migraine pain has been alleviated or eliminated. Additional doses may be taken during the seventy two hour period if migraine pain recurs.

The novel pharmaceutical compositions in accordance with the present invention are prepared by conventional means by methods known in the art. For example, there are known in the art methods for the preparation of known migraine palliatives, fully adaptable to the preparation of compositions of both known migraine palliatives and the thromboxane receptor antagonists and/or thromboxane synthetase inhibitors. Solid pharmaceutical compositions are provided in accordance with the present invention in the unit dosage form. A unit dosage for a solid pharmaceutical composition refers to the amount of each of the active ingredients which is administered in any one entity. Thus, the unit dosage form of a solid pharmaceutical composition makes reference to a discreet entity (e.g., a capsule, tablet, suppository, or



drug-releasing device), one or more of which entities contains an appropriate dosage for a single administration.

Accordingly, the novel solid pharmaceutical compositions in accordance with the present invention are adaptable to provide administration by oral, vaginal, rectal, intranasal, transdermal and buccal routes of administration. However, for parenteral routes (e.g., subcutaneous, intravenous, and intraarterial) the novel liquid pharmaceutical compositions in accordance with the present invention are provided. Also provided are novel liquid pharmaceutical compositions suitable for oral administration (e.g., syrups and elixirs). Each of these novel liquid pharmaceutical compositions in accordance with the present invention is prepared by methods known in the art.

For the liquid pharmaceutical compositions the active agents are provided in the same weight ratio as the intended respective daily dosages thereof for the patient being treated.

As a result of the employment of novel methods and compositions in accordance with the present invention, there is obtained surprisingly and unexpectedly improved results in the prophylaxis and/or symptomatic treatment of migraine patients. The instant use of thromboxane receptor antagonists and/or thromboxane synthetase inhibitors also provides surprisingly and unexpectedly improved results as compared to prior methods of treatment of migraine patients with known migraine palliatives. In particular, the present invention yields a surprisingly and unexpectedly better reduction in the frequency and/or severity of migraine headaches in those patients who suffer from two or more migraine attacks per month on a consistent basis, and an improved effectiveness in the mitigation of migraine pain and associated symptoms during the course of a migraine attack when such attacks do occur.

## **Description of the Preferred Embodiments**

### **Example 1**

An adult female migraineur has recurrent migraine attacks which occur with a frequency of four to six migraine headaches per month. These attacks consist of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing vapirost (GR32191), at a dose of 20 mg, twice daily on a continuous basis. After approximately one month of treatment with vapirost, the frequency of her migraine attacks begin to diminish, and within approximately three months of beginning treatment she is

experiencing only one to two mild migraine headaches per month. This prophylactic relief is superior to that which she has received in the past while using the standard medications indicated for prevention of migraine headaches.

**Example 2**

5 An adult female migraineur has recurrent migraine attacks which occur with a frequency of four to six migraine headaches per month. These attacks consist of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing isbogrel (CV-4151), at a dose of 50 mg, twice daily on a continuous basis. After approximately one month of treatment with isbogrel, the frequency of her migraine attacks begin to diminish,  
10 and within approximately three months of beginning treatment she is experiencing only one to two mild migraine headaches per month. This prophylactic relief is superior to that which she has received in the past while using the standard medications indicated for prevention of migraine headaches.

**Example 3**

15 An adult female migraineur has recurrent migraine attacks which occur with a frequency of four to six migraine headaches per month. These attacks consist of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing ridogrel (R-68070), at a dose of 300 mg, twice daily on a continuous basis. After approximately one month of treatment with ridogrel, the frequency of her migraine attacks  
20 begin to diminish, and within approximately three months of beginning treatment she is experiencing only one to two mild migraine headaches per month. This prophylactic relief is superior to that which she has received in the past while using the standard medications indicated for prevention of migraine headaches.

**Example 4**

25 An adult female migraineur has recurrent migraine attacks which occur with a frequency of four to six migraine headaches per month. These attacks consist of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing naproxen sodium at a dose of 550 mg and vapiprost (GR32191) at a dose of 20 mg, twice daily on a continuous basis. After approximately one month of treatment with naproxen sodium and  
30 vapiprost, the frequency of her migraine attacks begin to diminish, and within approximately three months of beginning treatment she is experiencing only one to two mild migraine

headaches per month. This prophylactic relief is superior to that which she has received in the past while using the standard medications indicated for prevention of migraine headaches.

**Example 5**

5 An adult female migraineur complains of a migraine attack consisting of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing vapiprost (GR32191) at a dose of 40 mg. Her symptoms start to diminish within one hour, and by three hours she is completely symptom free. No relapse over the next 48 hours is reported. Her pain is relieved more quickly, with longer uninterrupted relief, and with fewer side effects than when she takes her typical anti-migraine medication.

10 **Example 6**

An adult female migraineur complains of a migraine attack consisting of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing isbogrel (CV-4151) at a dose of 100 mg. Her symptoms start to diminish within one hour, and by three hours she is completely symptom free. No relapse over the next 15 48 hours is reported. Her pain is relieved more quickly, with longer uninterrupted relief, and with fewer side effects than when she takes her typical anti-migraine medication.

**Example 7**

An adult female migraineur complains of a migraine attack consisting of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single 20 oral tablet containing ridogrel (R-68070) at a dose of 600 mg. Her symptoms start to diminish within one hour, and by three hours she is completely symptom free. No relapse over the next 48 hours is reported. Her pain is relieved more quickly, with longer uninterrupted relief, and with fewer side effects than when she takes her typical anti-migraine medication.

**Example 8**

25 An adult female migraineur complains of a migraine attack consisting of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing sumatriptan at a dose of 12.5 mg and GR32191 at a dose of 40 mg. Her symptoms start to diminish within one hour, and by three hours she is completely symptom free. No relapse over the next 48 hours is reported. Her pain is relieved more quickly, with 30 longer uninterrupted relief, and with fewer side effects than when she takes either agent alone.

She experiences fewer adverse reactions to sumatriptan than if she receives standard (higher) doses, with particular reference to asthenia and flushing.

**Example 9**

5     An adult female migraineur complains of a migraine attack consisting of typical migraine headache pain, nausea and sensitivity to light and sound. She is dosed with a single oral tablet containing naproxen sodium at a dose of 550 and GR32191 at a dose of 40 mg. Her symptoms start to diminish within one hour, and by three hours she is completely symptom free. No relapse over the next 48 hours is reported. Her pain is relieved more quickly and with longer uninterrupted relief than when she takes either agent alone.

***What is claimed is:***

1. A method for preventing or treating a migraine headache in a patient susceptible to the development of migraine headaches or experiencing a migraine headache, which comprises:  
5 administering to said patient an amount of one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors effective to reduce the severity or duration of or prevent the occurrence of or mitigate the effects of a migraine headache.
2. A method according to claim 1, which comprises:  
10 administering to said patient of both a thromboxane receptor antagonist and/or a thromboxane synthetase inhibitor.
3. A method for treating a migraine headache according to claim 1, which further comprises:  
15 concomitantly administering to said patient an amount of one or more pharmacological agents selected from the group consisting of beta-adrenergic receptor blocking agents, tricyclic antidepressants, calcium antagonists, divalproex sodium, ergots and dihydroergotamine, serotonin receptor agonists, methylxanthines, non-steroidal anti-inflammatory agents, and dopamine agonists, effective in combination with said one or more thromboxane receptor  
20 antagonists and/or thromboxane synthetase inhibitors to reduce the severity or duration of a migraine headache.
4. A pharmaceutical composition comprising:  
(1) an amount of one or more thromboxane receptor antagonists and/or thromboxane  
25 synthetase inhibitors; and  
(2) an amount of one or more pharmacological agents selected from the group consisting of beta-adrenergic receptor blocking agents, tricyclic antidepressants, calcium antagonists, divalproex sodium, ergots and dihydroergotamine, serotonin receptor agonists, methylxanthines, non-steroidal anti-inflammatory agents, and dopamine agonists such as  
30 metoclopramide and domperidone, effective in combination with said one or more thromboxane

receptor antagonists and/or thromboxane synthetase inhibitors to reduce the severity or duration of a migraine headache.

5. In a method of treating a migraine headache, which consists essentially of administering  
5 to a patient suffering from a migraine headache a known migraine palliative selected from the group consisting of beta-adrenergic receptor blocking agents, tricyclic antidepressants, calcium antagonists, divalproex sodium, ergots and dihydroergotamine, serotonin receptor agonists, methylxanthines, and dopamine agonists, the improvement which comprises:

- 10 concomitantly administering to said patient an amount of one or more thromboxane receptor antagonists and/or thromboxane synthetase inhibitors effective in combination with said known migraine palliative to reduce the severity or duration of said migraine headache.

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<b>(57) Abstract</b>  The use of thromboxane receptor antagonists and/or thromboxane synthetase inhibitors in the prophylaxis and treatment of migraine is described. Further described are the use of thromboxane receptor antagonists and/or thromboxane synthetase inhibitors together with known migraine palliatives such as 5-HT <sub>1</sub> agonists, non-steroidal anti-inflammatory agents, and the like. Pharmaceutical compositions are described containing both known migraine palliatives and thromboxane receptor antagonists and/or thromboxane synthetase inhibitors.		

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04650

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/44 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 02494 A (SCHERING AG) 20 February 1992 (1992-02-20) page 12 ---	1
X	GB 2 038 821 A (PFIZER LTD) 30 July 1980 (1980-07-30) page 1 ---	1
X	WO 91 13062 A (FARMITALIA CARLO ERBA) 5 September 1991 (1991-09-05) page 13 ---	1
X	US 5 605 917 A (OGLETREE) 25 February 1997 (1997-02-25) examples 16-85 --- -/--	4

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

2 September 1999

Date of mailing of the international search report

08/09/1999

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/04650

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 19270 A (BASF AG) 12 November 1992 (1992-11-12) claims ----	4
X	WO 92 19182 A (UNIVERSITY OF TEXAS) 12 November 1992 (1992-11-12) claims -----	4

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